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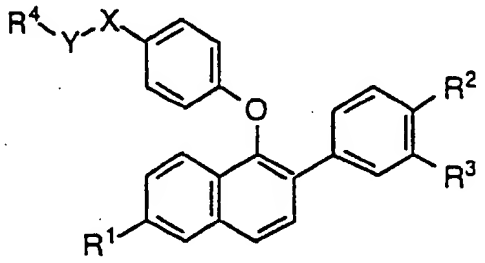
(54) 1-Aryloxy-2-arylnaphthyl compounds, intermediates, compositions, and methods

(57) The present invention provides a class of compounds having the structure



or a pharmaceutically acceptable salt where R^1 is hydrogen, hydroxy, alkoxy, alkoxycarbonyl, alkoxycarbonyloxy, aryloxycarbonyl, phenoxycarbonyloxy, or alkylsulfonyloxy; R^2 and R^3 are independently selected from hydrogen, halo, hydroxy, alkoxy, alkoxycarbonyl, alkoxycarbonyloxy, aryloxycarbonyl, phenoxycarbonyloxy, or alkylsulfonyloxy; R^4 is selected from hydroxy, alkoxy, cycloalkixy, 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidino, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, 1-hexamethyleneimino, and-OAr where where Ar is unsubstituted or substituted phenyl; X is selected from the group consisting of alkylene of two to four carbon atoms, -CH=CH-, $-CH_2CH=CH-$, and $-CH_2CH_2CH=CH-$; and Y is absent or is carbonyl, with the proviso that when Y is absent, R^4 may not be hydroxy, alkoxy, cycloalkoxy or aryloxy.

The compounds are selective estrogen receptor modulators (SERMOs) and are useful in the treatment of pathological conditions associated with estrogen deprivation or the abnormal response to endogenous estrogen.

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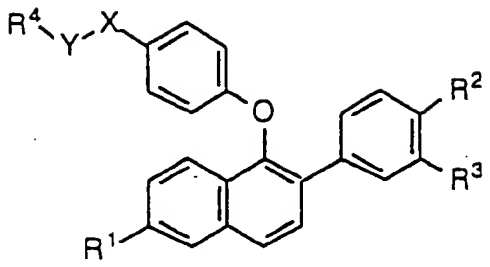

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or a pharmaceutically acceptable salt thereof wherein R^1 is selected from the group consisting of hydrogen, hydroxy, alkoxy of one to four carbon atoms, alkoxycarbonyl of two to seven carbon atoms, alkoxycarbonyloxy of two to seven carbon atoms, alkylsulfonyloxy, phenoxycarbonyloxy, and aryloxycarbonyl where the aryl portion is unsubstituted phenyl or is phenyl substituted with one or more substituents independently selected from the group consisting of halo, methyl, methoxy, nitro, and trifluoromethyl.

The substituents R^2 and R^3 are, independently selected from the group consisting of hydrogen, chloro, fluoro, hydroxy, alkoxy of one to four carbon atoms, alkoxycarbonyl of two to seven carbon atoms, alkoxycarbonyloxy of two to seven carbon atoms, alkylsulfonyloxy, phenoxycarbonyloxy, and aryloxycarbonyl where the aryl portion is unsubstituted phenyl or is phenyl substituted with one or more substituents independently selected from the group consisting of halo,methyl, methoxy, nitro, and trifluoromethyl.

The substituent R^4 is selected from the group consisting of hydroxy, alkoxy of one to six carbon atoms, cycloalkoxy of four to six carbon atoms, 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidino, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, 1-hexamethyleneimino, and aryloxy where wherein the aryl portion is unsubstituted phenyl or is phenyl substituted with one or more substituents independently selected from the group consisting of halo, methyl, methoxy, nitro, and trifluoromethyl.

The linking group X is selected from the group consisting of alkylene of two to four carbon atoms, -CH=CH-, $-CH_2CH=CH-$, and $-CH_2CH_2CH=CH-$; and Y is absent or is carbonyl, with the proviso that when Y is absent, R^4 may not be hydroxy, $-O(C_1-C_6$ alkyl), $-O(C_4-C_6$ cycloalkyl), or -OAr.

In another embodiment, the present invention provides a pharmaceutical compositions containing an effective amount of a compound of formula I, either as the sole active component, or together with an effective amount of estrogen or progestin.

In yet another embodiment, the present invention provides a method for the treatment of estrogen-dependent disease states.

As used throughout this specification and the appended claims, the the following terms have the ascribed meanings.

"Alkyl" denotes a monovalent group derived by the removal of a single hydrogen atom from a straight or branched hydrocarbon and is typified by methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, n-pentyl, iso-pentyl, n-hexyl, and the like.

"Alkylene" means a divalent group derived from methane, ethane or a straight or branched hydrocarbon of three or more carbon atoms by the removal of two hydrogen atoms, and is typified by such groups as methylene (i.e. $-CH_2-$), ethylene, propylene, and the like.

"Alkoxy" or "alkoxyl" means an alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom and is represented by groups such as methoxy, ethoxy, propoxy, and the like.

"Alkoxycarbonyl" denotes an alkoxy group, as defined above, connected to the parent molecular moiety through a carbonyl group and is typified by such groups as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, and the like.

"Alkoxycarbonyloxy" means an alkoxycarbonyl group, as defined above, connected to the parent molecular moiety through an oxygen atom and is represented by such groups as methoxycarbonyloxy, i.e. $-OC(O)OCH_3$, ethoxycarbonyloxy, and the like.

The term "alkylsulfonyloxy" denotes an alkyl group, as defined above, connected to the parent molecular moiety through a sulfonyl (i.e.$-SO_2-$) group, and then through an oxygen atom, and is typified by such groups as methylsulfonyloxy (i.e.$-O(SO_2)CH_3$), ethylsulfonyloxy, and the like.

"Aryloxycarbonyl" means an aryl group (within the context of the present invention, unsubstituted phenyl or phenyl substituted as defined above) attached through an oxygen atom and thence through a carbonyl group to the parent molecular moiety.

The term "cycloalkoxy" denotes a monovalent group derived from a cyclic aliphatic hydrocarbon by the removal

ıyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, butyl ester;
yl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, pentyl ester;
ıyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, pentyl ester;
yl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, hexyl ester;
ıyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, hexyl ester;
/l)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
yl)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
/l)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
yl)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
yloxy)phenyl]propenoic acid, ethyl ester;
-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
6-hydroxynaphth-1-yloxyl)phenyl]propenoic acid, ethyl ester;
6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
oxyophenyl)-6-methoxynaphth-1-yloxy)-phenyl]propenoic acid, ethyl ester;
xyophenyl)-6-hydroxynaphth-1-yloxy)-phenyl]propenoic acid, ethyl ester;
aphth-1-yloxy)phenyl]but-3-enoic acid, ethyl ester;
l)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, ethyl ester;
/l)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, ethyl ester;
l)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, pentyl ester;
/l)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, pentyl ester;
l)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
l)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
)naphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
l)naphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, phenyl ester;
l)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, phenyl ester;
)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, 4-methylphenyl ester;
l)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, 4-methylphenyl ester;
)naphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
l)naphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
ınaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
)naphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
-6-hydrxynaphth-1-yloxy)phenyl]propanoic acid, propyl ester;
)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, propyl ester;
-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid, pentyl ester;
)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, pentyl ester;
·hydroxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
·methoxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
·hydroxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
methoxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
/phenyl)-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
yphenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
-hydroxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
·methoxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
6-hydroxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
ɔhth-1-yloxy)phenyl]propanoic acid, butyl ester;
naphth-1-yloxy)phenyl]propanoic acid, butyl ester;
ıaphth-1-yloxy)phenyl]propanoic acid, butyl ester;
6-hydroxynaphth-1-yloxy)phenyl]propanoic acid, hexyl ester;
·6-methoxynaphth-1-yloxy)phenyl]propanoic acid, hexyl ester;
3-hydroxynaphth-1-yloxy)phenyl]butanoic acid, ethyl ester;
3-hydroxynaphth-1-yloxyl)phenyl]butanoic acid, ethyl ester;

1-[4-[3-(1-hexamethyleneimino)propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(N,N-dimethyl)propyl]phenoxy]-2-4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-pyrolidinyl)propyl]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(4-methoxyphenyl)naphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-phenyl-6-methoxynaphthalene;
1-[4-[3-(1-hexamethyleneimino)prop-2-enyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(4-chloro-phenyl)-6-methoxynaphthalene;
1-[4-[3-(N,N-dimethyl)prop-2-enyl]phenoxy]-2-(4-methoxy-phenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(4-methoxy-phenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(3-methoxy-phenyl)-6-methoxynaphthalene;
1-[4-[4-(1-pyrolidinyl)but-3-enyl]phenoxy]-2-(4-methoxy-phenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(4-methoxyphenyl)naphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-phenyl-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(3-fluorophenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(4-methoxyphenyl)naphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-phenyl-6-methoxynaphthalene;
1-[4-[4-(1-pyrolidinyl)butyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene; and
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(4-fluorophenyl)-6-methoxynaphthalene.

Preferred compounds of the present invention are compounds of Formula I above in which R^1, R^2 and R^3 are selected from halogen, hydroxy, and alkoxy, most preferably methoxy.

Particularly preferred compounds of the present invention are compounds in which Y is absent and R^4 is selected from 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidino, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, or 1-hexamethyleneimino, most preferably 1-pyrrolidinyl and 1-piperidinyl.

By virtue of their ability to act as so-called type II selective estrogen receptor modulators ("SERMs"), the compounds of the present invention are useful for the treatment of disease states associated with the deprivation or lack of estrogen as well as pathological conditions which are due to an aberrant physiological response to existing estrogen in estrogen sensitive tissues. SERMs, especially those of the current invention, have the property of being estrogen agonists in those cases where estrogen deprivation is a cause of pathology (mainly in non-sex related tissues) and simultaneously being antagonists of the pathologies caused by abnormal responses to endogenous estrogen (in sex related tissues).

Thus, compounds of the present invention are useful in the treatment of pathological conditions associated with estrogen deprivation such as bone loss or bone resorption, due to either menopause or ovariectomy.

Moreover, the compounds of the present invention are useful in the treatment of pathologies caused by abnormal responses to enogenous estrogen (in sex related tissues), including their usefulness in lower serum cholesterol levels.

A post-menopausal model was used in which the effects of different treatments upon circulating lipids and upon osteoporosis were determined. This model demonstrates the ulitity of the compounds of the current invention to treat pathologies caused by the deprivation of estrogen.

Seventy-five day old female Sprague Dawley rats (weight range of 200 to 225g) are obtained from Charles River Laboratories (Portage, MI). The animals are either bilaterally ovariectomized (OVX) or exposed to a Sham surgical procedure at Charles River Laboratories, and then shipped after one week. Upon arrival, they are housed in metal hanging cages in groups of 3 or 4 per cage and have *ad libitum* access to food (calcium content approximately 0.5%) and water for one week. Room temperature is maintained at 22.2° ± 1.7° C with a minimum relative humidity of 40%. The photoperiod in the room is 12 hours light and 12 hours dark.

Dosing Regimen Tissue Collection.

After a one week acclimation period (therefore, two weeks post-OVX) daily dosing with test compound is initiated. 17a-ethynyl estradiol or the test compound are given orally, unless otherwise stated, as a suspension in 1% carboxymethylcellulose or dissolved in 20% cyclodextrin. Animals are dosed daily for 4 days. Following the dosing regimen, animals are weighed and anesthetized with a ketamine: Xylazine (2:1, V:V) mixture and a blood sample is collected by cardiac puncture. The animals are then sacrificed by asphyxiation with CO_2, the uterus is removed through a midline incision, and a wet uterine weight is determined.

MCF-7 Proliferation Assay

MCF-7 breast adenocarcinoma cells (ATCC HTB 22) are maintained in MEM (minimal essential medium, phenol red-free, Sigma, St. Louis, MO) supplimented with 10% fetal bovine serum (FBS) (V/V), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES [(N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]10 mM), non-essential amino acids and bovine insulin (1 ug/mL) (maintenance medium). Ten days prior to assay, MCF-7 cells are switched to maintenance medium supplemented with 10% dextran coated charcoal stripped fetal bovine serum (DCC-FBS) assay medium) in place of 10% FBS to deplete internal stores of steroids. MCF-7 cells are removed from maintenance flasks using cell dissociation medium (Ca++/Mg++ free HBSS (phenol red-free) supplemented with 10 mM HEPES and 2 mM EDTA). Cells are washed twice with assay medium and adjusted to 80,000 cells/mL. Approximately 100 mL (8,000 cells) are added to flat-bottom microculture wells (Costar 3596) and incubated at 37° C in a 5% CO_2 humidified incubator for 48 hours to allow for cell adherence and equilibration after transfer. Serial dilutions of drugs or DMSO as a diluent control are prepared in assay medium and 50 mL transferred to triplicate microcultures followed by 50 mL assay medium for a final volume of 200 mL. After an additional 48 hours at 37° C in a 5% CO_2 humidified incubator, microcultures are pulsed with tritiated thymidine (1 uCi/well) for 4 hours. Cultures are terminated by freezing at -70° C for 24 hours followed by thawing and harvesting of microcultures using a Skatron Semiautomatic Cell Harvester. Samples are counted by liquid scintillation using a Wallac BetaPlace b counter. Activity of a compound of formula I in the present assay demonstrates that the compound is of potential for treating hormonally-dependent cancer, particularly breast cancer. For example, the compound of Example 3 inhibits cell growth in this assay with an IC_{50} 400 nM. The compound of Example 7 is extremely potent in this assay with an IC_{50} of 100 pM.

DMBA-Induced Mammary Tumor Inhibition

Estrogen-dependent mammary tumors are produced in female Sprague-Dawley rats which are purchased from Harlan Industries, Indianapolis, Indiana. At about 55 days of age, the rats receive a single oral feeding of 20 mg of 7,12-dimethylbenz[a]anthracene (DMBA). About 6 wooks after DMBA administration, the mammary glands are palpated at weekly intervals for the appearance of tumors. Whenever one or more tumors appear, the longest and shortest diameters of each tumor are measured with a metric caliper, the measurements are recorded, and that animal is selected for experimentation. An attempt is made to uniformly distribute the various sizes of tumors in the treated and control groups such that average-sized tumors are equivalently distributed between test groups. Control groups and test groups for each experiment contain 5 to 9 animals.

Compounds of Formula I are administered either through intraperitoneal injections in 2% acacia, or orally. Orally administered compounds are either dissolved or suspended in 0.2 mL corn oil. Each treatment, including acacia and corn oil control treatments, is administered once daily to each test animal. Following the initial tumor measurement and selection of test animals, tumors are measured each week by the above-mentioned method. The treatment and measurements of animals continue for 3 to 5 weeks at which time the final areas of the tumors are determined. For each compound and control treatment, the change in the mean tumor area is determined.

The present invention also provides a method of alleviating estrogen deprivation in women which comprises the aforementioned method using compounds of Formula I and further comprises administering to a woman an effective amount of estrogen or progestin. These treatments are particularly useful for treating osteoporosis and lowering serum cholesterol because the patient will receive the benefits of each pharmaceutical agent while the compounds of the present invention would inhibit undesirable side-effects of estrogen and progestin. Activity of these combination treatments in any of the post-menopausal tests, infra, indicates that the combination treatments are useful for alleviating the symptoms of post-menopausal symptoms in women.

Various forms of estrogen and progestin are commercially available. Estrogen-based agents include, for example, ethynyl estrogen (0.01 - 0.03 mg/day), mestranol (0.05 - 0.15 mg/day), and conjugated estrogenic hormones such as Premarin® (Wyeth-Ayerst; 0.3 - 2.5 mg/day). Progestin-based agents include, for example, medroxyprogesterone such as Provera® (Upjohn; 2.5 -10 mg/day), norethylnodrel (1.0 - 10.0 mg/day), and nonethindrone (0.5 - 2.0 mg/day). A preferred estrogen-based compound is Premarin, and norethylnodrel and norethindrone are preferred progestin-based agents.

The method of administration of each estrogen- and progestin-based agent is consistent with that which is known in the art. For the majority of the methods of the present invention, compounds of Formula I are administered continuously, from 1 to 3 times daily. However, cyclical therapy may especially be useful in the treatment of endometriosis or may be used acutely during painful attacks of the disease. In the case of restenosis, therapy may be limited to short (1-6 months) intervals following medical procedures such as angioplasty.

As used herein, the term "effective amount" means an amount of compound (formula I) of the present invention which is capable of alleviating, inhibiting, preventing, ameliorating, reversing, obviating, or lessening the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this

(continued)

Formulation 2: Tablets	
Ingredient	Quantity (mg/tablet)
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 2.5 - 1000 mg of active ingredient are made up as follows:

Formulation 3: Tablets	
Ingredient	Quantity (mg/tablet)
Active ingredient	25 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 ml dose are made as follows:

Formulation 4: Suspensions	
Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol	
Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

(continued)

Formulation 10: Combination Tablet	
Ingredient	Quantity (mg/capsule)
Premarin	1
Corn Starch NF	50
Povidone, K29-32	6
Avicel pH 101	41.50
Avicel pH 102	136.50
Crospovidone XL10	2.50
Magnesium Stearate	0.50
Cab-O-Sil	0.50

Compounds of the present invention are prepared, starting with the steps depicted in Reaction Scheme 1 in which R^{1a} is -H or $-OR^5$, where R^5 is a hydroxy protecting group, and R^{2a} and R^{3a} are -H, halo, or $-OR^5$.

Suitable hydroxyl protecting groups are those discussed in T. W. Greene, *et al.*, "Protective Groups in Organic Synthesis," 2nd Edition, John Wiley & Sons, Inc., New York, 1991.

formula 3. The hydrolysis step is accomplished via either acid or basic hydrolysis of the substrate in a polar protic solvent such as water or one or more solvents containing an alcohol such as methanol or ethanol. A cosolvent such as tetrahydrofuran (THF) or dioxane also may be added to the solution to aid solubility. Appropriate bases for this phase include sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like. Appropriate acids include, for example, hydrochloric acid, methanesulfonic acid, p-toluenesulfonic acid, and the like.

This final hydrolysis step, shown in Scheme 1, can be run at ambient temperature and is complete typically from 1 to about 12 hours. Completion of the hydrolysis step is followed by means of standard chromatographic techniques such as thin layer chromatography.

In the next step of Scheme 1, the phenol of formula 3 is first reacted with a base, followed by the addition of a 4-halobenzaldehyde in a polar aprotic solvent, under an inert atmosphere such as nitrogen, to give a biarylether of formula 4. This reaction is well known in the art and is carried out essentially as described by Yeager, G.W., et al., *Synthesis*, 63 (1991).

More particularly, 1 equivalent of a formula 3 compound is first treated with at least 1 equivalent of an alkali metal hydride, preferably sodium hydride, or carbonate in an appropriate solvent, followed by a dropwise addition of a 4-halobenzaldehyde, preferably 4-fluorobenzaldehyde, in the same solvent as used with the substrate.

Appropriate solvents for this reaction are those solvents or mixture of solvents which remain inert throughout the reaction. N,N-dimethylformamide (DMF), especially the anhydrous form thereof, is preferred. A preferred temperature range for this reaction is from about 30° C to about 100° C. Under the preferred reaction conditions, a formula IV compound is prepared in about 24 to about 48 hours.

Typical examples of compounds of formula 4 prepared by the process of Reaction Scheme 1 include:

1-(4-formylphenoxy)-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-(4-formylphenoxy)-2-(4-methoxyphenyl)naphthalene;
1-(4-formylphenoxy)-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-(4-formylphenoxy)-2-(3,4-di-methoxyphenyl)-6-methoxy-naphthalene;
1-(4-formylphenoxy)-2-(3-methoxyphenyl)naphthalene;
1-(4-formylphenoxy)-2-(4-chlorophenyl)-6-methoxynaphthalene;
1-(4-formylphenoxy)-2-(4-fluorophenyl)-6-methoxynaphthalene;
1-(4-formylphenoxy)-2-(4-chlorophenyl)naphthalene;
1-(4-formylphenoxy)-2-(4-fluorophenyl)naphthalene;
1-(4-formylphenoxy)-2-(3-fluorophenyl)-6-methoxynaphthalene;
1-(4-formylphenoxy)-2-(3-chlorophenyl)-6-methoxynaphthalene;
1-(4-formylphenoxy)-2-phenylnaphthalene;
1-(4-formylphenoxy)-2-(3-chlorophenyl)naphthalene;
1-(4-formylphenoxy)-2-(3-fluorophenyl)naphthalene;
1-(4-formylphenoxy)-2-(3-fluoro-4-methoxyphenyl)-6-methoxynaphthalene; and
1-(4-formylphenoxy)-2-(3-chloro-4-methoxyphenyl)-6-methoxynaphthalene.

The synthesis of the compounds of the present invention continues as depicted in Reaction Scheme 2 in which R^{1a}, R^{2a}, and R^{3a} have the meanings ascribed above, X^a is -CH=CH- or -CH_2CH=CH-, Y^a is -CO-; and R^{4a} is -O(C_1-C_6) alkyl, O(C_4-C_6) cycloalkyl, or -O Ar, where Ar is phenyl or substituted phenyl.

R^4 is a nitrogen containing moiety and Y is a methylene, i.e., R^4 and Y constitute an amino function, are synthesized from the compounds corresponding amides by reduction of the amide carbonyl.. This reduction may be accomplished with the use of reducing reagents, such as, $NaBH_4$, $LiAlH_4$, borane, and the like, in an inert solvent such as, THF, ether, CH_2Cl_2, etc., at ambient temperatures.

Reduction of any unsaturation in the linking group, X, is accomplished by techniques well know in the art such as catalytic reduction under hydrogen in the presence of a transition metal catalyst such as palladium, or platinum.

It should be noted that as before the reduction of the vinyl double (X) and the reduction of the carbonyl (Y) are independent of each other, i.e., there is no sequence restriction. Thus, an amine function can be synthesized before the reduction of the vinyl double or after.

Further, preferred compounds of formula I may be obtained by cleaving the R^5 and R^6 hydroxy protecting groups of formula Ia,b,c,e,f compounds via well known procedures. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, *Protective Groups in Organic Chemistry,* Plenum Press (London and New York, 1973); Green, T.W., Protective Groups *in Organic Synthesis,* Wiley, (New York, 1981); and *The Peptides,* Vol. I, Schrooder and Lubke, Academic Press (London and New York, 1965). Methods for removing preferred R^5 and/or R^6 hydroxy protecting groups, particularly methyl, are essentially as described in Example 7, *infra.*

Other preferred compounds of formula I are prepared by replacing the 6-, -3' and/or 4'-position hydroxy moieties, when present, with a moiety of the formula -O-CO-(C_1-C_6 alkyl), or -O-SO_2-(C_2-C_6 alkyl) via well known procedures. See, e.g., U.S. Pat. No. 4,358,593.

For example, when an -O-CO(C_1-C_6 alkyl) group is desired, a mono-, di-, or trihydroxy compound of formula I is reacted with an agent such as acyl chloride, bromide, cyanide, or azide, or with an appropriate anhydride or mixed anhydride. The reactions are conveniently carried out in a basic solvent such as pyridine, lutidine, quinoline or isoquinoline, or in a tertiary amine solvent such as triethylamine, tributylamine, methylpiperidine, and the like. The reaction also may be carried out in an inert solvent such as ethyl acetate, dimethylformamide, dimethylsulfoxide, dioxane, dimethoxyethane, acetonitrile, acetone, methyl ethyl ketone, and the like, to which at least one equivalent of an acid scavenger (except as noted below), such as a tertiary amine, has been added. If desired, acylation catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine may be used. See, e.g., Haslam, et al., *Tetrahedron,* 36:2409-2433 (1980).

The reactions are carried out at moderate temperatures, in the range from about -25° C to about 100° C, frequently under an inert atmosphere such as nitrogen gas. However, ambient temperature is usually adequate for the reaction to run.

Acylation of a 6-, -3' and/or 4'-position hydroxy group also may be performed by acid-catalyzed reactions of the appropriate carboxylic acids in inert organic solvents. Acid catalysts such as sulfuric acid, polyphosphoric acid, methanesulfonic acid, and the like are used.

The aforementioned R^1 and/or R^2 groups of formula I compounds also may be provided by forming an active ester of the appropriate acid, such as the esters formed by such known reagents such as dicyclohexylcarbodiimide(DCC), acylimidazoles, nitrophenols, pentachlorophenol, N-hydroxysuccinimide, and 1-hydroxybenzotriazole. See, e.g., *Bull. Chem.* Soc. *Japan,* 38:1979 (1965). and *Chem. Ber.,* 788 and 2024 (1970).

Each of the above techniques which provide -O-CO-(C_1-C_6 alkyl) moieties are carried out in solvents as discussed above. Those techniques which do not produce an acid product in the course of the reaction, of course, do not call for the use of an acid scavenger in the reaction mixture.

When a formula I compound is desired in which the 6-,-3' and/or 4'-position hydroxy group of a formula I compound is converted to a group of the formula -O-SO_2-(C_2-C_6 alkyl), the mono-, di-, or trihydroxy compound is reacted with, for example, a sulfonic anhydride or a derivative of the appropriate sulfonic acid such as a sulfonyl chloride, bromide, or sulfonyl ammonium salt, as taught by King and Monoir, *J. Am. Chem. Soc.,* 97:2566-2567 (1975). Such reactions are carried out under conditions such as were explained above in the discussion of reaction with acid halides and the like.

Although the free-base or acid forms of formula I compounds can be used in the methods of the present invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. Thus, the compounds used in the methods of this invention form pharmaceutically acceptable acid or base addition salts with a wide variety of organic and inorganic acids and bases, and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids, such as aliphatic monc and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, b-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinna-

quinone (DDQ), 13.7 g (60.3 mmol) was added. The reaction was refluxed for 1.5 hours, after cooling to ambient temperature, 200 mL of CH_2Cl_2 was added. The reaction mixture was washed four times with 200 mL portions of 0.2 N NaOH, twice with 200 mL portions of water, and the resulting solution was dried with Na_2SO_4 and evaporated to a solid. This yielded the intermediate phenolic acetate which was hydroyzed by dissolving the solid in 200 mL of MeOH-THF (1:1) (v/v) and added an excess amount of MeONa. An orange precipitate formed which was filtered off. The resulting filtrate was acidified with to pH 4 with 5 N HCl and diluted with 200 mL of water. The solution was extracted three times with 100 mL portions of EtOAc and organic layers combind, dried with Na_2SO_4, evaporated to dryness. The final product was crystallized from EtOAc-hexane, which yielded 4.24g of the title compound as a white solid.
^{1}H NMR: Consistent with the proposed structure.
MS: M/e=280-(M)FD
Analysis: Calc. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75 Fd: C, 76.83; H, 5.90

Preparation 4

Preparation of 2-(3-methoxythenyl)-6-methoxy-1-tetralone

In a manner similar to that used in Preparation 2, the title compound was prepared as a tan solid, mp 81-82-C.

Preparation 5

Preparation of 1-hydroxy-2-(3-methoxythenyl-6-methoxynaphthalene

In a manner similar to that used in Preparation 3, the title compound was prepared as a clear oil.
^{1}H NMR ($CDCl_3$) 8.19 ppm (d, J=9.1 Hz, 1H); 7.51-6.94 ppm (m, 8H); 5.91 ppm (s, 1H); 3.94 ppm (s, 3H)
MS m/c=230 (M) FD
Analysis Calc. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75 Found: C, 76.91; H, 5.81.

Preparation 6

Preparation of 1-hydroxy-2-(3-methoxyphenyl)naphthalene

In a manner analogous to Preparations 1-3, the title compound was prepared as a tan, amorphous solid.
^{1}H NMR: 8.30 ppm (m, 1H); 7.80 ppm (m, 1H); 7.57-7.45 ppm (m, 4H); 7.40 ppm (d, J=7.1 Hz, 1H); 7.35 ppm (d, J=6.0 Hz, 1H); 7.06 ppm (s, 1H0; 6.97 ppm (dd, J=6.0 Hz, 1H); 6.00 ppm (s, 1H); 3.90 ppm (s, 1H)
MS: m/e=250 (M) FD
Analysis: Calc. for $C_{17}H_{14}O_2$-0.21 mol EtOAc: C, 79.52; H,
5.93 Found: C, 79.72; H, 5.63

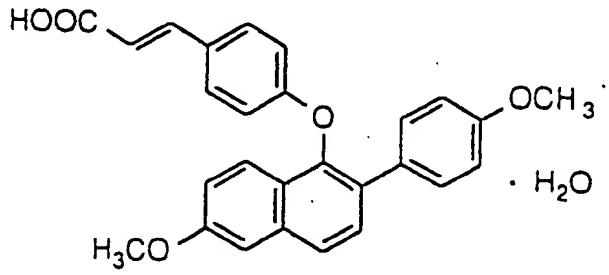
Preparation 7

1-(4-formylphenoxy)-2-(4-methoxyphenyl)-6-methoxynaphthalene

To a solution of [2-(4-methoxyphenyl)]-6-methoxynaphthyl-1-ol (3.57 g, 12.75 mmol) in 180 mL of anhydrous N, N-dimethylformamide under N2 at ambient temperature was added sodium hydride (535 mg, 13.38 mmol, 60% dispersion in mineral oil) in small portions. After stirring for 10 min., 4-flourobenzaldehyde (3.20 g, 25.50 mmol) was added. The resulting mixture was heated to 70° C for 36 hours. Upon cooling to ambient temperature, the solvent was removed *in vacuo*. The residue was then distributed between ethyl acetate/water. The layers were separated and the organic was washed several times with water. The organic layer was finally dried (sodium sulfate) and concentrated *in vacuo* to an oil. Chromatography (90:10 hexanes/ethyl acetate) provided 2.06 g (48%) of 1-(4-formyl)phenoxy-2-(4-methoxyphenyl)-6-methoxynaphthalene as a white solid that was crystallized from methanol. Data for 1-(4-formyl)phenoxy-2-(4-methoxyphenyl)-6-methoxynaphthalene: mp 120-121° C.
^{1}H NMR ($CDCl_3$) d 9.80 (s, 1H), 7.78 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 9.2, 2.6 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 3.95 (s, 3H), 3.78 (s, 3H). FD mass spec: 384. *Anal.* Calcd. for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24. Found: C, 78.32; H, 5.24.

Example 2

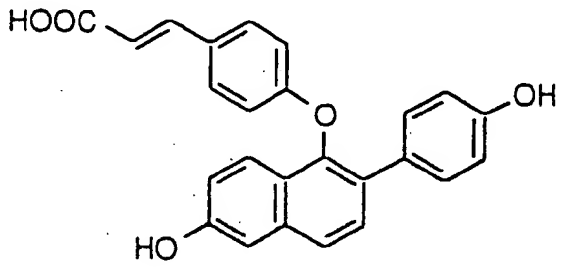
Preparation of 3-[4-((2-(4-methoxyphenyl)-6-methoxynaphth-1-yl)oxy)phenyl]propenoic acid, hydrate



A solution was prepared of 771 mg (1.7 mmol) of 3-[4-((2-(4-methoxyphenyl)-6-methoxynaphth-1-yl)oxy)phenyl] propenoic acid, ethyl ester (prepared as described in Example 1 above) in 10 mL of ethanol, 7 mL of tetrahydrofuran, and 10 mL of 1 N NaOH. The reaction was warmed on a steam bath to clearify the solution. After one hour, an additional 2 mL of 2 N NaOH was added and the reaction was warmed. The reaction was quenched by addition of cold 2 N HCl. The aqueous mixture was extracted three times with ether. The combined ether extracts were washed with brine, dried with Na2SO4, and evaporated to dryness. The product was purified by chromatography on a silica gel column eluted with MeOH-$CHCl_3$ (1:99) (v/v). This yielded 704 mg of the title compound as a tan amorphous solid. mp 97-100°C.
^1H NMR: Consistent with the proposed structure
MS: m/e=426 (M) FD
Analysis: Calc. for $C_{27}H_{22}O_5$-HOH: C, 72.96; H, 5.44; Found: C, 73.03; H, 5.20.

Example 3

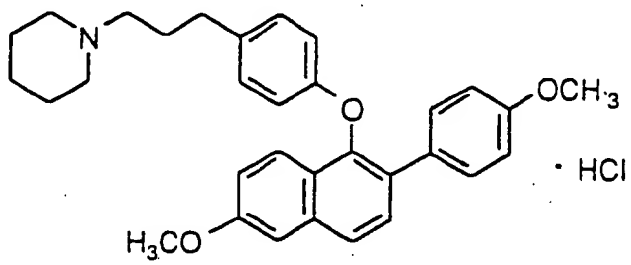
Preparation of 3-[4-((2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yl)oxy)phenyl]propenoic acid



A solution was prepared of 658 mg (1.54 mmol) of 3-[4-((2-(4-methoxyphenyl)-6-methoxynaphth-1-yl)oxy)phenyl] propenoic acid hydrate in 10 mL of dichloromethane. The solution was cooled to 5°C and 0.44 mL (4.7 mmol) of BBr_3 was added. The reaction was allowed to proceed for one hour at 0° C under a nitrogen atmosphere. The reaction was quenched by pouring into water and extracting three times with ethyl acetate. The combined ethyl acetate extracts were washed with water, brine, dried with Na2SO4, and evaporated to an oily, red solid. The product was purified by chromatography on a silica gel column eluted with MeOH-$CHCl_3$ (1:99) (v/v). This yielded 489 mg of the title compound as a yellow, amorphous solid, mp 150-153°C.
^1H NMR: Consistent with the proposed structure.
MS: m/e=398 (M) FD
Analysis: Calc. for $C_{25}H_{18}O_5$: C, 75.37; H, 4.55 Found: C, 75.64; H, 4.65.

Example 6

Preparation of 1-[4-[3-(1-Piperidinyl)propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene Hydrochloride



A solution was prepared of 470 mg (1 mmol) of 1-[4-[3-(1-piperidinyl)2-propenyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene (prepared as described in Example 5 above) in 25 mL of ethyl acetate and 75 mL of ethanol. To this solution was added 480 mg of 5% Pd/C, and the mixture was placed in a Parr hydrogenation apparatus under H_2 at a pressure of 4 psi. After one hour, the reaction mixture was filtered to remove the catalyst and the residue was evaporated to dryness. The residue was dissolved in 10 mL of ethyl acetate and ether saturated with HCl was added until no further precipiate formed. The solvents were removed by evaporation. This yielded 429 mg of the title compound as a white amorphous solid, mp 192-194°C.

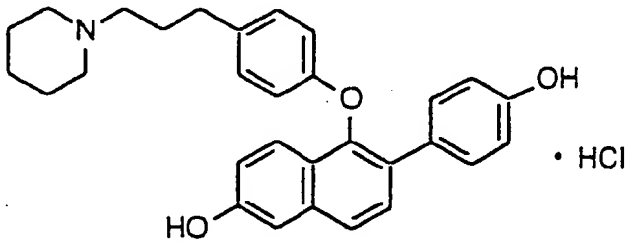
^{1}H NMR: Consistent with the proposed structure.

MS: m/e=481 (M-HCl) FD

Analysis: Calc. for $C_{32}H_{35}NO_3$-HCl: C, 74.19; H, 7.00; N, 2.70 Found: C, 73.90; H, 6.95; N, 2.72.

Example 7

Preparation of 1-[4-[3-(1-Piperidinyl)propyl]phenoxy]-2-(4-hydroxyphenyl)-6-hydroxynaphthalene Hydrochloride



A solution of 315 mg (0.61 mmol) of 1-[4-[3-(1-piperidinyl)2-propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene hydrochloride (prepared as described in Example 7 above) in 20 mL of dichloromethane was prepared, cooled to 5° C, and 0.17 mL (1.83 mmol) of BBr_3 was added. The reaction was allowed to proceed at 5°C under a nitrogen atmosphere for thirty minutes. The reaction was quenched by pouring into a saturated solution of aqueous $NaHCO_3$ The aqueous suspension was extracted with CH_2Cl_2 five times. The combined CH_2Cl_2 extract was washed with brine, dried with Na_2SO_4, and evaporated to dryness. The residue was dissolved in EtOAc-EtOH and diethyl ether, saturated with HCl, was added until no further precipitate formed. This yielded 271 mg of the title compound as a white solid, mp 222-224°C.

^{1}H NMR: Consistent with the proposed structure.

MS: m/e=454 (M-Cl) FD

Analysis: Calc. for $C_{30}H_{31}NO_3$-HCl: C, 73.53; H, 6.58; N, 2.86 Found: C, 73.75; H, 6.49; N, 2.92.

Claims

1. A compound of formula 1

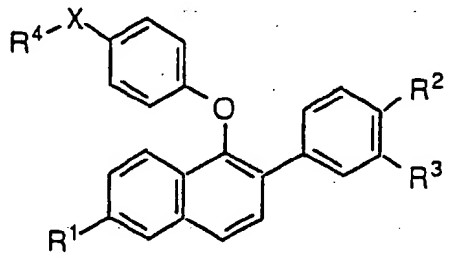
R^4 is selected from the group consisting of hydroxy,
alkoxy of one to six carbon atoms,
cycloalkoxy of four to six carbon atoms,
1-piperidinyl,
1-pyrrolidinyl,
methyl-1-pyrrolidinyl,
dimethyl-1-pyrrolidino,
4-morpholino,
dimethylamino,
diethylamino,
diisopropylamino,
l-hexamethyleneimino, and
aryloxy where wherein the aryl portion is selected
from the group consisting of
unsubstituted phenyl, and
phenyl substituted with one or more
substituents independently selected
from the group consisting of

halo,
methyl,
methoxy,
nitro, and
trifluoromethyl;

X is selected from the group consisting of alkylene of two to four carbon atoms,
-CH=CH-,
$-CH_2CH=CH-$, and
$-CH_2CH_2CH=CH-$; and

Y is absent or is carbonyl, with the proviso that when
Y is absent, R^4 may not be hydroxy, $-O(C_1-C_6$ alkyl), $-O(C_4-C_6$ cycloalkyl), or -OAr.

2. A compound as defined by Claim 1 having the structure



wherein R^1, R^2, R^3, and R^4 and X are as defined therein.

3. A compound as defined by Claim 1 having the structure

3-[4-(2-(3-methoxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid;
3-[4-(2-(3-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid;
3-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid;
3-[4-(2-(4-methoxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid:
3-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid;
3-[4-(2-(4-chlorophenyl)-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid;
3-[4-(2-(4-chlorophenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid;
3-[4-(2-(3-fluorophenyl)-6-hydroxynaphth-1-yloxy)phenyl]propanoic acid;
3-[4-(2-(3-fluorophenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid;
4-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]butanoic acid;
4-[4-(2-(4-methoxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]butanoic acid; and
4-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]butanoic acid; or

a pharmaceutically acceptable salt thereof.

6. A compound according to Claim 4 selected from the group consisting of

3-[4-(2-(3-hydroxyphenyl)-6-hydroxynaphth-1-ylyloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(3-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(3-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, propyl ester;
3-[4-(2-(3-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, propyl ester;
3-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, butyl ester;
3-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, butyl ester;
3-[4-(2-(3-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, pentyl ester;
3-[4-(2-(3-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, pentyl ester;
3-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, hexyl ester;
3-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, hexyl ester;
3-[4-(2-(3-hydroxyphenyl)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(3-methoxyphenyl)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-hydroxyphenyl)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-methoxyphenyl)naphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-phenylnaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-chlorophenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-chlorophenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(3-fluorophenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(3-fluorophenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-fluorophenyl)-6-hydroxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(4-fluorophenyl)-6-methoxynaphth-1-yloxy)phenyl]propenoic acid, ethyl ester;
3-[4-(2-(3-fluoro-4-methoxyophenyl)-6-methoxynaphth-1-yloxy)-phenyl]propenoic acid, ethyl ester;
3-[4-(2-(3-fluoro-4-hydroxyophenyl)-6-hydroxynaphth-1-yloxy)-phenyl]propenoic acid, ethyl ester;
4-[4-(2-(3-fluorophenyl)naphth-1-yloxy)phenyl]but-3-enoic acid, ethyl ester;
4-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, ethyl ester;
4-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, ethyl ester;
4-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, pentyl ester;
4-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, pentyl ester;
4-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
4-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
4-[4-(2-(4-hydroxyphenyl)naphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
4-[4-(2-(4-methoxyphenyl)naphth-1-yloxy)phenyl]but-3-enoic acid, cyclohexyl ester;
4-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, phenyl ester;
4-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, phenyl ester;
4-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, 4-methylphenyl ester;
4-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, 4-methylphenyl ester;
3-[4-(2-(3-hydroxyphenyl)naphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
3-[4-(2-(3-methoxyphenyl)naphth-1-yloxy)phenyl]propanoic acid, ethyl ester;
3-[4-(2-(4-hydroxyphenyl)naphth-1-yloxy)phenyl]propanoic acid, ethyl ester;

4-[4-(2-(3-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, 1-piperidinylamide;
4-[4-(2-(4-hydroxyphenyl)-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, 1-piperidinylamide;
4-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, 1-piperidinylamide;
4-[4-(2-(4-hydroxyphenyl)naphth-1-yloxy)phenyl]but-3-enoic acid, 1-piperidinylamide;
4-[4-(2-(4-methoxyphenyl)naphth-1-yloxy)phenyl]but-3-enoic acid, 1-piperidinylamide;
4-[4-(2-phenyl-6-hydroxynaphth-1-yloxy)phenyl]but-3-enoic acid, 1-piperidinylamide;
4-[4-(2-phenyl-6-methoxynaphth-1-yloxy)phenyl]but-3-enoic acid, 1-piperidinylamide;
3-[4-(2-(4-hydroxyphenyl)naphth-1-yloxy)phenyl]propanoic acid, N,N-diethylamide;
3-[4-(2-(4-methoxyphenyl)naphth-1-yloxy)phenyl]propanoic acid, N,N-diethylamide;
3-[4-(2-(3-hydroxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, 1-piperidinylamide;
3-[4-(2-(3-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, 1-piperidinylamide;
3-[4-(2-(4-hydroxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, 1-piperidinylamide; and
3-[4-(2-(4-methoxyphenyl)-6-methoxynaphth-1-yloxy)phenyl]propanoic acid, 1-piperidinylamide.

9. A compound according to Claim 2 selected from the group consisting of

1-[4-[3-(piperidin-1-yl)propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)propyl]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)propyl]phenoxy]-2-(3,4-dimethoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)propyl]phenoxy]-2-(3-fluorophenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)propyl]phenoxy]-2-(4-chlorophenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)propyl]phenoxy]-2-(4-methoxyphenyl)naphthalene;
1-[4-[3-(1-pyrolidinyl)propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(N,N-dimethyl)propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-hexamethyleneimino)propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(N,N-dimethyl)propyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-pyrolidinyl)propyl]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(4-methoxyphenyl)naphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-phenyl-6-methoxynaphthalene;
1-[4-[3-(1-hexamethyleneimino)prop-2-enyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[3-(1-piperidinyl)prop-2-enyl]phenoxy]-2-(4-chlorophenyl)-6-methoxynaphthalene;
1-[4-[3-(N,N-dimethyl)prop-2-enyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(3 -methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-pyrolidinyl)but-3-enyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(4-methoxyphenyl)naphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-phenyl-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)but-3-enyl]phenoxy]-2-(3-fluorophenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(3-methoxyphenyl)-6-methoxynaphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(4-methoxyphenyl)naphthalene;
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-phenyl-6-methoxy-naphthalene;
1-[4-[4-(1-pyrolidinyl)butyl]phenoxy]-2-(4-methoxyphenyl)-6-methoxynaphthalene; and
1-[4-[4-(1-piperidinyl)butyl]phenoxy]-2-(4-fluorophenyl)-6-methoxynaphthalene.

10. A pharmaceutical formulation comprising an effective amount of a compound as defined by Claim 1 in combination with a pharmaceutically acceptable carrier.

11. A pharmaceutical formulation according to Claim 10 further comprising an effective amount of a compound selected from the group consisting of estrogen and progestin.

12. A compound according to any one of Claims 1 to 9 or a pharmaceutically acceptable salt thereof for use in medicine.

13. Use of a compound of Claim 1 in the manufacture of a medicament for inhibiting bone loss or bone resorption.

14. Use according to Claim 13 wherein said bone loss or bone resorption is due to menopause or ovariectomy.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 30 7994

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	EP 0 733 620 A (ELI LILLY AND COMPANY) * the whole document * ---	1,10	C07D295/08 C07C43/295 C07C47/575
Y	EP 0 731 093 A (ELI LILLY AND COMPANY) * the whole document * ---	1,10	A61K31/445
Y	EP 0 729 951 A (ELI LILLY AND COMPANY) * the whole document * ---	1,10	
Y	EP 0 703 228 A (ELI LILLY AND COMPANY) * the whole document * -----	1,10	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	19 December 1997	Kyriakakou, G

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
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A: technological background
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